REMARKS

1. Objections to the Specification

The examiner objected to the specification for reference to Figure 11 when only Figures 1 through 10 were filed with the application. Applicants thank the examiner for pointing out this error. The amendments to the specification made herein to page 96 correct this error by referencing Figure 10.

The applicants acknowledge the examiner's remarks regarding use of trademarks and submit that the specification will be amended as deemed appropriate once allowable subject matter has been indicated.

2. The Double Patenting Rejection

Claims 1-14 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-38 and 51-62 of U.S. Patent No. 6,319,906, and over claims 1-18, and 20-37 of U.S. Patent No. 6,077,833. Applicants respectfully traverse, but in order to expedite prosecution, applicants submit herewith a terminal disclaimer disclaiming any term beyond that of U.S. Patent No. 6,319,906 and U.S. Patent No. 6,077,833.

3. The 102(e) Rejection

Claims 1, 6, and 8 through 10 were rejected under 35 USC 102(e) as being directed to subject matter assertedly anticipated by the disclosure of Stinchcomb, et al., US Patent 5,877,021. ("the '021 patent"). The '021 patent is cited for its alleged disclosure, *inter alia*, of (i) use of nucleic acid based techniques for graft tolerance, autoimmune disorders, allergies, to inhibit synthesis of B7-1, B7-2, B7-3, CD40, and ICAM-1, these techniques including use of (a) ribozymes, (b) antisense, (c) triplex DNA *etc.*; (ii) ribozymes to B7-1 and B7-2 transcripts; (iii) hammerhead ribozymes 13-40 nucleotides against B7-1 and B7-2; (iv) delivery in liposomes, etc. and (v) topical administration. The examiner then concluded that the '021 patent teaches "each and every aspect of the instant invention" of the rejected claims and therefore anticipated the subject matter of these claims. The applicants respectfully traverse.

The '021 patent disclosure mentions antisense nucleic acid molecules only in passing (See *e.g.*, col. 5, line 66, to col. 6, line 6; col. 6, line 39-44) and distinguishes molecules of this type from ribozymes in that antisense molecules are expressly defined as being "non-enzymatic." (Col. 6, line 39-40). Beyond this disclosure, the '021 patent specification is completely silent with respect to the invention recited in the presently rejected claims. To the extent that antisense molecules are significant to the disclosure of the '021 patent at all, the only possible reason for even mentioning a "non-enzymatic" antisense sequence is it's ability to localize the enzymatic moiety of a ribozyme, and nothing in the disclosure states or suggests that the a molecule without the enzymatic component will possess any therapeutic value. The '021 specification certainly does not disclose that a completely "non-enzymatic" antisense molecule having 8-30 nucleobases can be used topically to treat any type of skin disorder, and therefore cannot anticipate the subject matter of the broadest claim in the present application.

The applicants submit therefore that, absent demonstration of anticipation of the broadest claim by a single reference, it is axiomatic that all dependent claims are also free from anticipation by the same cited reference. Accordingly, the rejection of claims 1, 6, and 8 through 10 over the disclosure of the '021 patent must be withdrawn.

4. The 103 Rejection

Claims 1 through 14 were rejected under 35 USC 103(a) as being directed to subject matter assertedly rendered obvious by the disclosure of the '021 patent or Freeman, *et al.* US Patent No. 5,942,607 ("the '607 patent"), "either in view of Abramowicz (WO 94/17773) and Cooper (WO 93/24134 A1)." In a telephone conversation with the examiner on June 30, the undersigned was advised that proper reading of the rejection is based on the disclosure of either the '021 patent or the '607 patent, in view of the disclosures of Abramowicz and Cooper. The applicant would like to thank the examiner for this clarification

The '021 patent was cited for reasons described above in the 102(e) rejection. The '607 patent was cited for disclosure of (i) antisense to B7-1 and B7-2 as a means to block expression in B lymphocytes, (ii) two specific antisense oligonucleotides, and (iii) administering antisense to block B cell antigen function to block T cell activation, thereby permitting treatment of autoimmune diseases. The examiner admits that neither the '021 patent nor the '607 patent disclose the antisense molecules specifically recited in claim 1, the

modifications recited in dependent claims, use of these compounds for treatment of the specifically recited skin disorders, and pharmaceutical compositions comprising the antisense molecules and an anti-inflammatory or immunosuppressive agent. The applicants also add that neither reference discloses topical administration of antisense molecules either in isolated form or in pharmaceutical compositions.

The examiner further relied on the disclosure of Abramowicz for assertedly disclosing the use of IL-10 to block B7 and ICAM-1 expression on monocytes and for use of IL-10 to prevent/treat various atopic disease states. Cooper was cited for assertedly describing use of oligomeric compounds for treating cellular hyperproliferation disorders.

Starting with the references individually, the experimental work carried out in Cooper is limited to cell culture analysis using oligomers directed to IL-1α, IL-1β, or IL-1 receptor antagonist. Nothing in these results, however, demonstrates (i) that the observed results are predictive of their use in an *in vivo* application, and (ii) that results from two different types of keratinocyte culture [p. 22, lines 10-32] are accepted models for identifying candidate topical therapeutics and that these models have been useful and successful to predict *in vivo* results. Whether these results can be reproduced *in vivo* is left undecided in Cooper, and even if they could be reproduced, there is no evidence that the same degree of inhibition of cell proliferation would provide any therapeutic effect much less the results recited in the rejected claims. As a result, the worker of skill in the art cannot predict what, if any, degree of success can be expected from *in vivo* use of Cooper's oligomer compounds against IL-1 or IL-1 receptor antagonist, or oligomers against any other specific target or targets.

The disclosure of Abramowicz does not correct the deficiency in the Cooper disclosure. While Abramowicz does in fact provide *in vivo* experimental data relating to use of IL-10 and the observed effects, the specific *in vivo* effects on B7 expression are not readily apparent from the disclosure. While the examiner is correct in stating that Abramowisc describes IL-10 protein to block expression of B7 on monocytes, Abramowicz demonstrates at page 40, second complete paragraph, that recombinant IL-10 "modified neither B7 expression by transfected fibroblasts nor CD28 expression by purified T cells." Even though this description of results is not entirely clear, it does suggest that IL-10 control of B7 expression is dependent of the experimental conditions and that negative regulation of B7 expression may not, in fact, be predictable in all cell types after *in vivo* administration.

To the extent that the '021 patent briefly mentions antisense technology, the specification in its entirety relates to use of ribozymes. As discussed above, the applicants submit that the '021 patent disclosure is unrelated to antisense methods as claimed herein. In addition, while the '607 patent does mention topical administration of B7 antisense and goes so far as to disclose two antisense oligonucleotides, the disclosure is at best only predictive because no experimental data is provided. Moreover, the disclosure addresses topical administration only in the context of proposed treatment of viral disorders, and does not address the indications specifically recited in the rejected claims.

The applicants submit it is arguable that the worker of skill in the art may be motivated to combine and modify the art cited by the examiner to produce the invention as presently claimed, but the combination of the art does not provide any expectation to the skilled worker that the combination/modification will successfully give the claimed invention. Absent evidence of a reasonable expectation of success, a rejection under 103 cannot be maintained, and the applicants submit that no expectation of success can be derived from this combination of the examiner's evidence. Accordingly, the rejection of claims 1 through 14 under 103 must be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. According, the Examiner is respectfully requested to pass this application to issue.

Dated: July 10, 2003

Respectfully submitted,

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